Journal of Microbiology, Immunology and Infection 57 (2024) 446—456

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Epidemiology and antimicrobial susceptibility profiles of Enterobacterales causing bloodstream infections before and during COVID-19 pandemic: Results of the Study for Monitoring Antimicrobial Resistance Trends (SMART) in Taiwan, 2018—2021

Yu-Lin Lee [a,b,c], Chun-Eng Liu [d], Hung-Jen Tang [e], Yu-Tsung Huang [f], Yao-Shen Chen [g], Po-Ren Hsueh [h,i,j,k,*], SMART Taiwan Group

[a] *Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan*
[b] *School of Medicine, Chung Shan Medical University, Taichung, Taiwan*
[c] *Ph.D Program in Medical Biotechnology, National Chung-Hsing University, Taichung, Taiwan*
[d] *Department of Internal Medicine, Changhua Christian Hospital, Changhua, Taiwan*
[e] *Department of Medicine, Chi Mei Medical Center, Tainan, Taiwan*
[f] *Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*
[g] *Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[h] *Departments of Laboratory Medicine and Internal Medicine, China Medical University Hospital, Taichung, Taiwan*
[i] *School of Medicine, China Medical University, Taichung, Taiwan*
[j] *Ph.D Program for Ageing, School of Medicine, China Medical University, Taichung, Taiwan*
[k] *Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*

Received 7 September 2023; received in revised form 1 March 2024; accepted 4 April 2024
Available online 7 April 2024

* Corresponding author. Departments of Laboratory Medicine and Internal Medicine, China Medical University Hospital, No. 2, Yude Rd., North Dist., Taichung 404332, Taiwan.
E-mail address: hsporen@gmail.com (P.-R. Hsueh).

https://doi.org/10.1016/j.jmii.2024.04.004

KEYWORDS
Enterobacterales;
Multidrug resistance;
Carbapenem resistance;
COVID-19;
Imipenem-relebactam;
Meropenem-vaborbactam

Abstract *Background:* The coronavirus disease 2019 (COVID-19) pandemic has contributed to the spread of antimicrobial resistance, including carbapenem-resistant Enterobacterales.
Methods: This study utilized data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) surveillance program in Taiwan. Enterobacterales from patients with bloodstream infections (BSIs) were collected and subjected to antimicrobial susceptibility testing and β-lactamase gene detection using a multiplex PCR assay. Statistical analysis was conducted to compare susceptibility rates and resistance genes between time periods before (2018—2019) and during the COVID-19 pandemic (2020—2021).
Results: A total of 1231 Enterobacterales isolates were collected, predominantly *Escherichia coli* (55.6%) and *Klebsiella pneumoniae* (29.2%). The proportion of nosocomial BSIs increased during the COVID-19 pandemic (55.5% vs. 61.7%, $p < 0.05$). Overall, susceptibility rates for most antimicrobial agents decreased, with Enterobacterales from nosocomial BSIs showing significantly lower susceptibility rates than those from community-acquired BSIs. Among 123 Enterobacterales isolates that underwent molecular resistance mechanism detection, ESBL, AmpC β-lactamase, and carbapenemase genes were detected in 43.1%, 48.8% and 16.3% of the tested isolates, respectively. The prevalence of carbapenemase genes among carbapenem-resistant Enterobacterales increased during the pandemic, although the difference was not statistically significant. Two novel β-lactamase inhibitor combinations, imipenem-relebactam and meropenem-vaborbactam, preserved good efficacy against Enterobacterales. However, imipenem-relebactam showed lower *in vitro* activity against imipenem-non-susceptible Enterobacterales than that of meropenem-vaborbactam.
Conclusions: The COVID-19 pandemic appears to be associated with a general decrease in antimicrobial susceptibility rates among Enterobacterales causing BSIs in Taiwan. Continuous surveillance is crucial to monitor antimicrobial resistance during the pandemic and in the future.

Introduction

Carbapenem resistance in Enterobacterales, mostly *Klebsiella pneumoniae* and *Escherichia coli*, is a global public health threat.[1,2] These bacteria are commonly associated with health care-associated infections, including bloodstream infections (BSIs), particularly in immunocompromised patients.[3—6] BSIs caused by carbapenem-resistant Enterobacterales (CRE) are associated with higher mortality rates than infections caused by carbapenem-susceptible strains.[7,8] Resistance to carbapenems, which are considered last-line antibiotics, limits the treatment options for these infections, leading to poorer outcomes.[9—11] A recent study investigated 32,100 patients who had BSIs and found that the proportions of appropriate therapy were 55.3% for CRE species. Compared with inappropriate empirical therapy, appropriate empirical antimicrobial therapy was associated with an approximately half reduction in the in-hospital risk of death for gram-negative rods, including CRE.[12]

The coronavirus disease 2019 (COVID-19) pandemic has had a significant impact on the prevalence and spread of CRE. Several studies have reported an increase in the incidence of CRE infections during the pandemic.[13—15] This increase in CRE is attributed to various factors, including the high rates of antimicrobial agent utilization in COVID-19 patients and the relatively low rate of co or secondary infections.[15] The overuse of antibiotics in COVID-19 patients has contributed to the development of antibiotic-resistant bacterial strains, including carbapenem-resistant strains.[16,17] Taiwan identified the first imported case of a COVID-19 patient returning from Wuhan, China, through onboard quarantine on January 21, 2020.[18] From 2020 to 2022, a total of 8,872,955 confirmed cases and 15,253 fatality cases due to COVID-19 were reported in Taiwan.[19] In the early pandemic, effective policies and strict interventions were implemented, including universal mask wearing, hand hygiene, border control, quarantine of COVID-19 patients, and travel and gathering restrictions. Therefore, the number of COVID-19 cases was only 823 and 16,303 in 2020 and 2021, respectively.[20,21] A recent review also concluded that Taiwan maintained relatively low death rates of COVID-19 infection and that the economy outperformed amid the COVID-19 crisis in that actual gross domestic product growth (4.3%) was higher than had been predicted (2.0%).[22] However, the impact of the COVID-19 pandemic on antimicrobial resistance in Taiwan is still not known.

The Study for Monitoring Antimicrobial Resistance Trends (SMART) is a surveillance program used to investigate the *in vitro* antimicrobial susceptibility of clinically important pathogens causing intra-abdominal infections since 2002.[23—25] Since 2018, the SMART program has extended surveillance to include pathogens causing BSIs. The purpose of this study was to evaluate the resistance trend among Enterobacterales isolates from patients with BSIs before and during the COVID-19 pandemic in Taiwan.

Materials and methods

Bacterial isolates and identification

During the period of 2018–2021, nine hospitals participated in the SMART surveillance program in Taiwan. All nine participant hospitals included in this study are major tertiary referral hospitals during the COVID-19 pandemic. Each hospital was required to gather a maximum of 50 g-negative isolates every year, including Enterobacterales, from patients with bloodstream infections (BSIs) throughout the study duration. All the collected isolates were then sent to the central laboratory of International Health Management Associates, Inc. (IHMA) in Schaumburg, Illinois, USA, where they were stored for further testing. The central laboratory employed MALDI-TOF spectrometry to verify bacterial identification. In the study, community-acquired infections were defined as isolates collected within 48 h of hospitalization from patients who exhibited symptoms and signs of infection upon admission. Conversely, hospital-acquired isolates were defined as those collected 48 h or more after hospitalization from patients who initially did not display any symptoms or signs of infection. The Institutional Review Board or Research Ethics Committees of each participating hospital approved the SMART program, and informed consent was waived due to the minimal risk posed to the participating patients.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was conducted at IHMA (Schaumburg, IL) using the broth microdilution method, with frozen panels prepared specifically at IHMA. The MIC interpretive criteria were based on the guidelines provided by the Clinical and Laboratory Standards Institute (CLSI) (M100-S33, 2023).[26] Minimum inhibitory concentrations (MICs) were determined for various tested agents, including amikacin, aztreonam, cefepime, ceftazidime, ceftriaxone, ceftolozane/tazobactam, colistin, ertapenem, imipenem, levofloxacin, meropenem, and piperacillin/tazobactam. The MICs of imipenem-relebactam and meropenem-vaborbactam were determined for isolates collected in 2021. Isolates, excluding Morganellaceae and *Serratia* spp., underwent additional molecular testing for the presence of genes encoding common β-lactamases, such as ESBLs and carbapenemases, if the isolates exhibited nonsusceptibility to imipenem (MIC $\geq$2 mg/L), imipenem-relebactam (MIC $\geq$2 mg/L), and/or ceftolozane/tazobactam (MIC $\geq$4 mg/L). Molecular gene detection for Morganellaceae was excluded due to the intrinsic nonsusceptibility of the Morganellaceae family (including *Proteus* species, *Morganella* species, and *Providencia* species) to imipenem, primarily attributed to their weak affinity to penicillin binding proteins (PBPs) or porin loss, rather than carbapenemase production.[23,27] Similarly, *Serratia* spp. isolates were not characterized, as genes encoding acquired β-lactamases were rarely found in the species.[23,27]

Detection of β-lactamase genes

A single colony grown overnight on a blood agar plate (Thermo Fisher Scientific, Waltham, MA, USA) at 35 °C was collected for the extraction of genomic DNA. Whole genomic DNA extraction was performed using the QIAamp DNA Mini Kit and a QIAcube instrument (Qiagen, Valencia, CA). A multiplex PCR assay was conducted to rapidly detect the presence of ESBL genes (bla_{TEM}, bla_{SHV}, bla_{CTX-M}, bla_{VEB}, bla_{PER}, and bla_{GES}), AmpC β-lactamase genes (bla_{CMY}, bla_{DHA}, bla_{FOX}, bla_{MOX}, bla_{ACC}, bla_{MIR}, and bla_{ACT}) and carbapenemase genes (bla_{KPC}, bla_{VIM}, bla_{IMP}, bla_{NDM}, and bla_{OXA}) in the selected Enterobacterales, following previously described protocols.[23,24,27]

Statistical analyses

Statistical analyses were conducted using MedCalc software (MedCalc Software Ltd, Los Angeles, CA, USA). Categorical variables were compared using either the chi-square test or Fisher's exact test. All tests were two-tailed, and statistical significance was defined as a p value less than 0.05.

Results

Characteristics of Enterobacterales isolates

A total of 1231 Enterobacterales isolates from participating hospitals were collected during 2018–2021, including *E. coli* (n = 685, 55.6%), *K. pneumoniae* (n = 360, 29.2%), *Enterobacter cloacae* complex (n = 62, 5.0%), *Proteus mirabilis* (n = 34, 2.8%), *Serratia marcescens* (n = 27, 2.2%), *Klebsiella aerogenes* (n = 22, 1.8%), *Klebsiella oxytoca* (n = 10, 0.8%), *Klebsiella variicola* (n = 9, 0.7%), *Morganella morganii* (n = 7, 0.6%), *Salmonella* (n = 5, 0.4%), *Enterobacter bugandensis* (n = 4, 0.3%), *Citrobacter koseri* (n = 4, 0.3%), and *Citrobacter freundii* (n = 2, 0.2%). The ranking of species in community-acquired BSIs was similar to that in nosocomial BSIs, but the distribution was significantly different. The proportion of *E. coli* was lower in nosocomial BSIs than in community-acquired BSIs (62.2% vs. 51.0%, $p < 0.05$), but *K. pneumoniae* (26.2% vs. 31.4%, $p < 0.05$), *E. cloacae* complex (2.9% vs. 6.5%, $p < 0.05$), *S. marcescens* (0.8% vs. 3.2%, $p < 0.05$) and *K. aerogenes* (0.6% vs. 2.6%, $p < 0.05$) isolates were more often collected from patients with nosocomial BSIs. Notably, the proportion of isolates collected from nosocomial BSIs increased during the COVID-19 pandemic (61.7% [370/600] vs. 55.5% [350/631], $p = 0.027$). A higher proportion of Enterobacterales isolates from nosocomial BSIs met the criteria for molecular resistance analysis compared to isolates from community-acquired BSIs (14.7% [106/720] vs. 3.3% [17/511], $p < 0.001$) in the study. Notably, genes encoding extended-spectrum beta-lactamase (ESBL) and carbapenemase were predominantly detected among isolates from nosocomial BSIs (Table 1).

Table 1 Distribution of bacterial species, sample sources and resistance mechanisms among Enterobacterales causing bacteremia in patients from whom isolates were obtained within 48 h (<48 h) or after 48 h (≥48 h) of hospitalization.

	<48 h (n = 511)	≥48 h (n = 720)	*p* value
Species			
Escherichia coli	318 (62.2)	367 (51.0)	<0.001
Klebsiella pneumoniae	134 (26.2)	226 (31.4)	
Proteus mirabilis	20 (3.9)	14 (1.9)	
Enterobacter cloacae complex	15 (2.9)	47 (6.5)	
Klebsiella oxytoca	5 (1.0)	5 (0.7)	
Klebsiella variicola	4 (0.8)	5 (0.7)	
Salmonella spp.	4 (0.8)	1 (0.1)	
Serratia marcescens	4 (0.8)	23 (3.2)	
Klebsiella aerogenes	3 (0.6)	19 (2.6)	
Citrobacter koseri	2 (0.4)	2 (0.3)	
Enterobacter bugandensis	1 (0.2)	3 (0.4)	
Morganella morganii	1 (0.2)	6 (0.8)	
Citrobacter freundii	0 (0)	2 (0.3)	
Years			0.027
2018–2019	281 (55.0)	350 (48.6)	
2020–2021	230 (45.0)	370 (51.4)	
Resistance mechanisms			
Isolates fulfilled criteria of resistance mechanism survey	17 (3.3)	106 (14.7)	<0.001
ESBL-positive	4 (23.5%)[a]	49 (46.2%)[a]	<0.001
AmpC ß-lactamase-positive	8 (47.0%)[a]	52 (49.1%)[a]	0.878
Carbapenemase-positive	1 (5.9%)[a]	19 (17.9%)[a]	<0.001

[a] The percentage indicates the number of isolates with detected ESBL or carbapenemase genes among isolates that fulfilled the criteria for the resistance mechanism survey.

Antimicrobial susceptibility and trend dynamics before and during the COVID-19 pandemic

For all 1231 Enterobacterales isolates, the antimicrobial agents with susceptibility rates greater than 90% included amikacin (using CLSI 2023 criteria), ertapenem, meropenem, and meropenem. In addition, a total of 101 (8.2%, 101/1231) Enterobacterales isolates were resistant to colistin (MIC of colistin ≥4 mg/L). Isolates from nosocomial BSIs had significantly lower susceptibility rates than those collected from community-acquired BSIs for most antimicrobial agents, including aztreonam, cefepime, ceftazidime, ceftolozane/tazobactam, ceftriaxone, levofloxacin, and piperacillin/tazobactam (Fig. 1.). The species distribution before and during the COVID-19 pandemic was similar: more than half were *E. coli*, followed by *K. pneumoniae* and *E. cloacae* (Fig. 2.). Although the difference did not reach statistical significance, isolates collected during 2020–2021 had generally lower susceptibility rates than those collected before the COVID-19 pandemic (Fig. 1.). In Table 2, we list the susceptibility rates of isolates collected pre-COVID-19 and during the COVID-19 pandemic. The difference was more often observed for *K. pneumoniae* and other Enterobacterales than *E. coli*. For levofloxacin in nosocomial BSIs, the susceptibility rates of *K. pneumoniae* and other Enterobacterales decreased from 63.7% to 80.3% during 2018–2019 to 55.6% and 60.6% during 2020–2021, respectively.

The numbers of CRE were 44, 40, and 21 according to the MIC values of ertapenem, imipenem, and meropenem, respectively. Among 44 ertapenem-resistant Enterobacterales isolates, *K. pneumoniae* was most common (61.4%, 27/44), followed by *E. coli* (18.2%, 8/44), *E. cloacae* complex (13.6%, 6/44), *S. marcescens* (4.5%, 2/44), and *K. aerogenes* (2.3%, 1/44).

Two novel β-lactamase inhibitor combinations, imipenem-relebactam and meropenem-vaborbactam, were tested for 307 Enterobacterales collected in 2021. Five isolates (1.6%) were resistant to imipenem-relebactam, including 2 *M. morganii*, 2 *P. mirabilis*, and 1 *S. marcescens*. In addition, a total of 17 (5.5%) isolates showed intermediate susceptibility to imipenem-relebactam, including 9 *P. mirabilis*, 3 *K. pneumoniae*, 2 *M. morganii*, 1 *E. cloacae* complex, 1 *E. coli*, and 1 *S. marcescens*. For meropenem-vaborbactam, only one *K. pneumoniae* strain had intermediate susceptibility (MIC, 8 mg/L).

Detection of β-lactamase-encoding genes in Enterobacterales

A total of 123 Enterobacterales isolates fulfilled the criteria for further molecular resistance mechanism surveys, including 1 *C. koseri*, 20 *E. cloacae* complex, 30 *E. coli*, 12 *K. aerogenes*, 57 *K. pneumoniae*, and 2 *S. maecescens* isolates. ESBL-, AmpC ß-lactamase- and carbapenemase-related genes were detected in 43.1% (53/123), 48.8% (60/123) and 16.3% (20/123) of all tested isolates, respectively. Among 123 isolates, 63 were collected during 2018–2019, and 60 were collected during 2020–2021. The percentage of isolates with ESBL and carbapenemase genes increased from 38.1% (24/63) and 12.7% (8/63) during 2018–2019 to 48.3% (8/63) and 20% (12/60) during 2020–2021. Instead, the AmpC β-lactamase carriage rates decreased from 55.6% (35/63) to 41.7% (25/60) between the two study periods (Fig. 3.). The detected ESBL genes included bla_{SHV} (21), bla_{CTX-M} (40), and bla_{VEB} (1); AmpC β-lactamase genes included bla_{CMY-2} (29) and bla_{DHA} (31); and carbapenemase genes included bla_{KPC} (11), bla_{OXA-48} (4), bla_{NDM} (2), and bla_{IMP} (2). The distribution of β-lactamase genes in separate periods of this study is illustrated in Fig. 4.

For 93 Enterobacterales isolates that were not susceptible to imipenem (MIC ≥2 mg/L), 55 strains underwent genotypic tests for carbapenemase genes because the Morganellaceae family (including Proteus species, Morganella species, and Providencia species) was excluded according to the protocol. Among the tested Enterobacterales, 34.5% (19/55) of isolates had carbapenemase genes. All 19 isolates with detected carbapenemase genes and their MICs to tested antimicrobial agents are summarized in Table 3. *K. pneumoniae* was the most common pathogen to harbour carbapenemase genes among

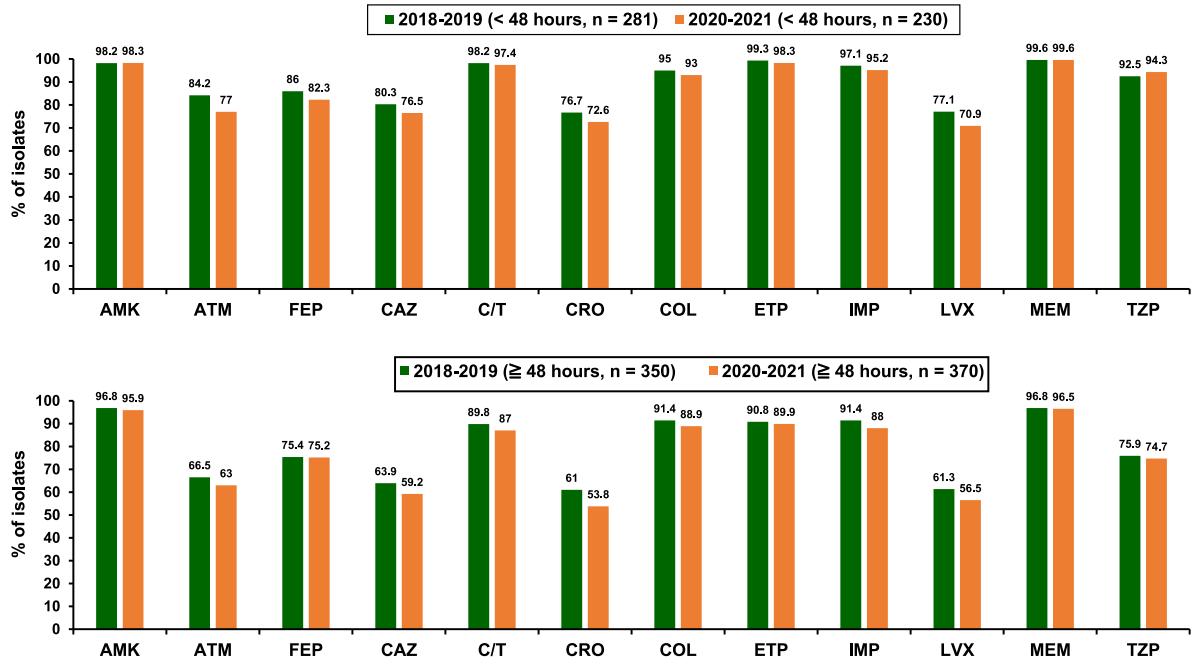

Figure 1. *In vitro* susceptibility rates to antimicrobial agents of Enterobacterales collected from patients with bloodstream infections who were hospitalized at <48 or ≥48 h in the Study for Monitoring Antimicrobial Resistance Trends (SMART) in Taiwan, 2018–2021. AMK, amikacin; ATM, aztreonam; FEP, cefepime; CAZ, ceftazidime; C/T, ceftolozane/tazobactam; CRO, ceftriaxone; COL, colistin; ETP, ertapenem; IMP, imipenem; LVX, levofloxacin; MEM, meropenem; TZP, piperacillin/tazobactam.

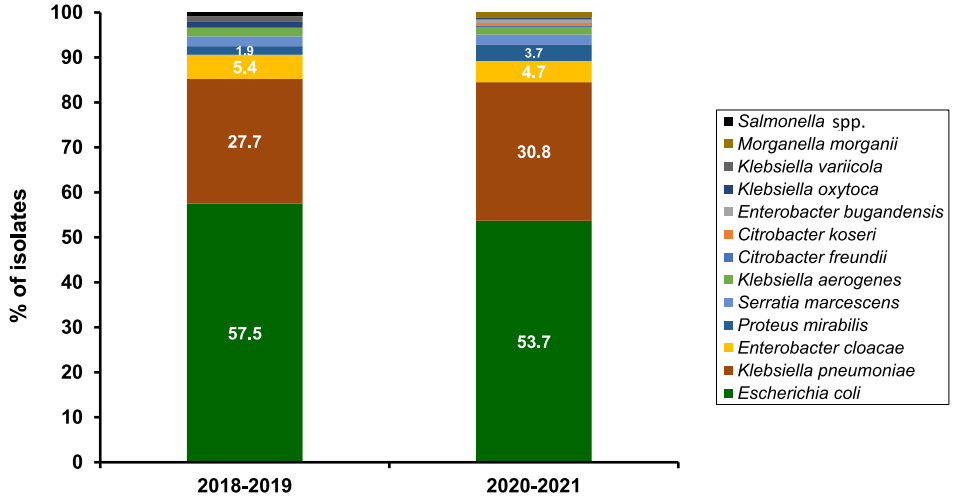

Figure 2. Species distribution (%) of Enterobacterales collected from patients with bloodstream infections in the Study for Monitoring Antimicrobial Resistance Trends (SMART) in Taiwan, 2018–2021.

all Enterobacterales, including 9 bla_{KPC-2}, 1 bla_{KPC-17}, 1 bla_{KPC-91}, and 4 bla_{OXA-48} genes. The ratio of carbapenemase genes detected in imipenem-non-susceptible *K. pneumoniae* strains was 39.5% (15/38) in our study. Notably, one *E. cloacae* with the bla_{IMP-8} gene collected in 2021 was susceptible to all carbapenems, and another *E. cloacae* isolate collected in 2018 had bla_{IMP-8} but was susceptible to meropenem in this surveillance.

In addition, only one *K. pneumoniae* strain had intermediate susceptibility to meropenem-vaborbactam and harboured bla_{SHV} and bla_{CTX-M} but no carbapenemase gene. Isolates with resistance to imipenem-relebactam, including *M. morganii*, *P. mirabilis*, and *S. marcescens*, were excluded from the molecular analysis according to the study protocol. For isolates with intermediate susceptibility to imipenem-relebactam, only one *K. pneumoniae* isolate had bla_{OXA-48}, and none had MβL genes such as bla_{NDM} or bla_{IMP}. Interestingly, one *E. cloacae* strain collected in 2021 had the bla_{IMP} gene but was susceptible to imipenem, meropenem, imipenem/relebactam, and meropenem/vaborbactam.

Table 2 The antimicrobial susceptibility of *Escherichia coli*, *Klebsiella pneumoniae* and other Enterobacterales from patients with bloodstream infections (BSIs) in the Study for Monitoring Antimicrobial Resistance Trends (SMART) in Taiwan between 2018-2019 and 2020–2021.

Organism/agent/year of isolation	No. (%) of isolates susceptible to the indicated antimicrobial agent			
	Community-acquired BSI (<48 h)		Hospital-acquired BSI (≥48 h)	
Organism/antibacterial	2018–2019	2020–2021	2018–2019	2020–2021
E. coli (n = 685)	(n = 176)	(n = 142)	(n = 187)	(n = 180)
Amikacin	176 (100)	141 (99.3)	187 (100)	178 (98.9)
Aztreonam	139 (79)	100 (70.4)	116 (62)	115 (63.9)
Cefepime	144 (81.8)	108 (76.1)	132 (70.6)	139 (77.2)
Ceftazidime	134 (76.1)	101 (71.1)	118 (63.1)	117 (65)
Ceftolozane/tazobactam	174 (98.9)	141 (99.3)	170 (90.9)	172 (95.6)
Ceftriaxone	124 (70.5)	93 (65.5)	109 (58.3)	99 (55)
Colistin[a]	175 (99.4)	142 (100)	180 (96.3)	179 (99.4)
Ertapenem	174 (98.9)	142 (100)	177 (94.7)	175 (97.2)
Imipenem	175 (99.4)	142 (100)	182 (97.3)	179 (99.4)
Imipenem/relebactam (n = 158)	–	66/66 (100)	–	91/92 (98.9)
Levofloxacin	125 (71)	97 (68.3)	101 (54)	100 (55.6)
Meropenem	175 (99.4)	142 (100)	183 (97.9)	180 (100)
Meropenem/vaborbactam (n = 158)	–	66/66 (100)	–	92/92 (100)
Piperacillin/tazobactam	164 (93.2)	136 (95.8)	152 (81.3)	156 (86.7)
K. pneumoniae (n = 360)	(n = 73)	(n = 61)	(n = 102)	(n = 124)
Amikacin	73 (100)	61 (100)	98 (96.1)	117 (94.4)
Aztreonam	69 (94.5)	55 (90.2)	73 (71.6)	73 (58.9)[b]
Cefepime	69 (94.5)	58 (95.1)	82 (80.4)	89 (71.8)
Ceftazidime	62 (84.9)	53 (86.9)	65 (63.7)	63 (50.8)
Ceftolozane/tazobactam	72 (98.6)	60 (98.4)	87 (85.3)	96 (77.4)
Ceftriaxone	64 (87.7)	52 (85.2)	67 (65.7)	65 (52.4)
Colistin[a]	73 (100)	60 (98.4)	99 (97.1)	116 (93.5)
Ertapenem	73 (100)	59 (96.7)	87 (85.3)	99 (79.8)
Imipenem	71 (97.3)	58 (95.1)	90 (88.2)	103 (83.1)
Imipenem/relebactam (n = 94)	–	29/29 (100)	–	62/65 (95.4)
Levofloxacin	64 (87.7)	45 (73.8)[b]	65 (63.7)	69 (55.6)
Meropenem	73 (100)	60 (98.4)	96 (94.1)	112 (90.3)
Meropenem/vaborbactam (n = 94)	–	29/29 (100)	–	64/65 (98.5)
Piperacillin/tazobactam	66 (90.4)	57 (93.4)	72 (70.6)	72 (58.1)
Other *Enterobacterales* (n = 186)	(n = 32)	(n = 27)	(n = 61)	(n = 66)
Amikacin	32 (100)	25 (92.6)	59 (96.7)	63 (95.5)
Aztreonam	29 (90.6)	22 (81.5)	43 (70.5)	45 (68.2)
Cefepime	29 (90.6)	23 (85.2)	50 (82)	50 (75.8)
Ceftazidime	30 (93.8)	22 (81.5)	40 (65.6)	39 (59.1)
Ceftolozane/tazobactam	30 (93.8)	23 (85.2)	47 (77)	54 (81.8)
Ceftriaxone	28 (87.5)	22 (81.5)	37 (60.7)	35 (53)
Colistin[a]	19 (59.4)	12 (44.4)	41 (67.2)	34 (51.5)
Ertapenem	32 (100)	25 (92.6)	54 (88.5)	59 (89.4)
Imipenem	27 (84.4)	19 (70.4)	48 (78.7)	44 (66.7)
Imipenem/relebactam (n = 55)	–	12/15 (80)	–	25/40 (62.5)
Levofloxacin	28 (87.5)	21 (77.8)	49 (80.3)	40 (60.6)[b]
Meropenem	32 (100)	27 (100)	60 (98.4)	65 (98.5)
Meropenem/vaborbactam (n = 55)	–	15/15 (100)	–	40/40 (100)
Piperacillin/tazobactam	30 (93.8)	24 (88.9)	42 (68.9)	49 (74.2)

[a] Percentage of colistin indicated the number of isolates with intermediate MIC according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (MIC ≤2 mg/L).[26]

[b] Data from 2020 to 2021 were significantly lower than data from 2018 to 2019 ($p < 0.05$).

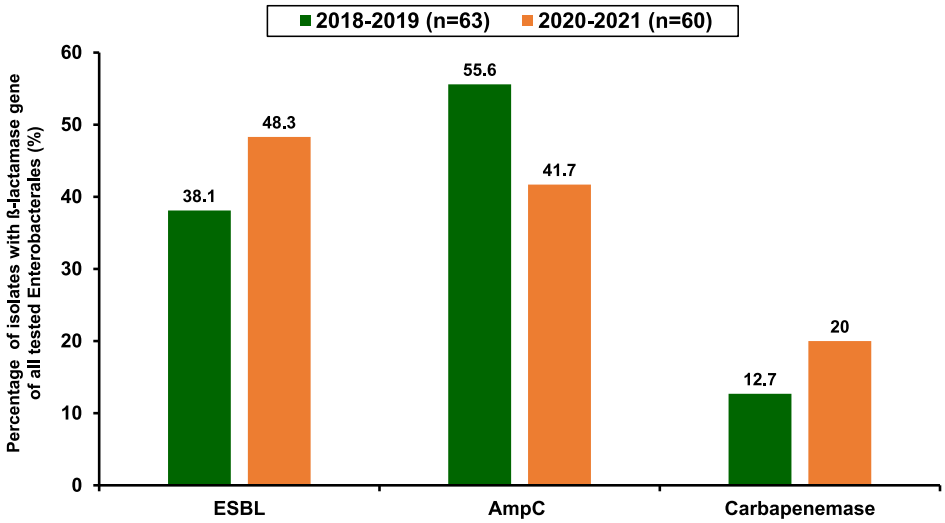

Figure 3. Distribution of detected β-lactamase genes, including extended-spectrum β-lactamases (ESBL), AmpC β-lactamases (AmpC), and carbapenemases (CBPM), between two study periods, 2018—2019 and 2020—2021, in the Study for Monitoring Antimicrobial Resistance Trends (SMART) in Taiwan.

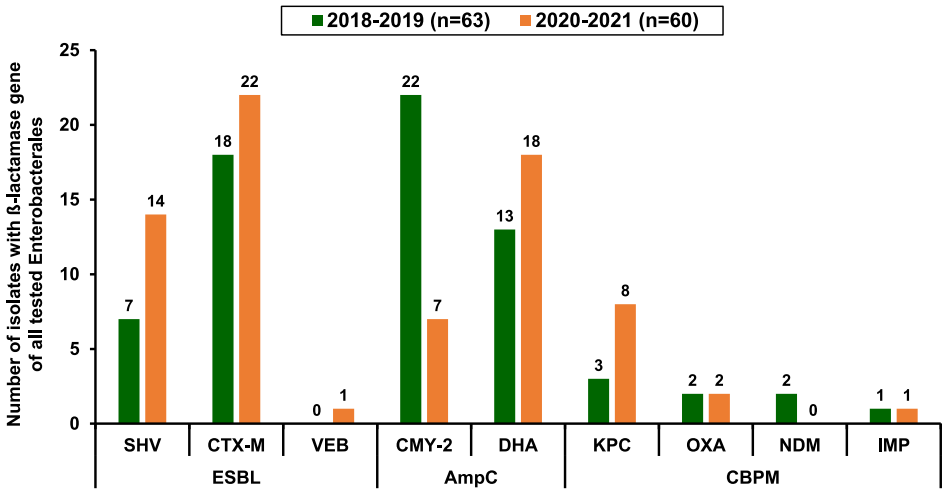

Figure 4. Number of detected β-lactamase genes belonging to extended-spectrum β-lactamases (ESBL), AmpC β-lactamases (AmpC), and carbapenemases (CBPM) between two study periods, 2018—2019 and 2020—2021, in the Study for Monitoring Antimicrobial Resistance Trends (SMART) in Taiwan.

Discussion

During the COVID-19 pandemic, antibiotic resistance has continued to rise in many countries, with some even experiencing an exacerbation of the trend.[28—31] In our study, we utilized data from a continuous surveillance program, the SMART study, to evaluate the impact of the COVID-19 pandemic on the *in vitro* susceptibility of Enterobacterales isolates from patients with bloodstream infections in Taiwan from 2018 to 2021. Although the differences were not statistically significant, we observed reduced susceptibility to almost every tested antimicrobial agent. The ratio of ESBL and carbapenemase genes detected among CRE also increased from 38.1% (24/63) and 12.7% (8/63) during 2018—2019 to 48.3% (29/60) and 20% (15/60) during 2020—2021. Two novel β-lactamase inhibitor combinations, imipenem-relebactam and meropenem-vaborbactam, demonstrated excellent activity against Enterobacterales in the present study.

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, is a global health crisis that began in late 2019 and has continued to impact the world until now.[19,22] The increased use of antibiotics, disruptions in health care systems, and changes in infection prevention and control practices have contributed to the emergence and spread of multidrug-resistant Enterobacterales, including CRE, during the pandemic.[28,29] In a recent systematic review, the COVID-19 pandemic was found to have no association with changes in the incidence density (incidence rate ratio 0.99, 95% confidence interval [CI]: 0.67—1.47) or proportion (risk

Table 3 List of minimum inhibitory concentrations (MICs, mg/L) of antimicrobial agents against Enterobacterales with detected carbapenemase genes collected from patients with bloodstream infections in the Study for Monitoring Antimicrobial Resistance Trends (SMART) in Taiwan, 2018—2021.

Organism	Year	CBPM	AMK	ATM	FEP	CAZ	C/T	CRO	COL	ETP	IPM	LVX	MEM	TZP
2018—2019														
Escherichia coli	2018	NDM-5	4	16	16	16	8	8	1	4	8	4	8	64
Escherichia coli	2018	NDM-1	4	16	16	16	8	8	1	4	8	4	8	64
Klebsiella pneumoniae	2018	KPC-2	32	16	16	16	8	8	1	4	8	4	8	64
Klebsiella pneumoniae	2018	KPC-2	8	16	16	16	8	8	2	4	8	4	8	64
Klebsiella pneumoniae	2018	OXA-48	32	16	16	16	8	8	4	4	2	4	2	64
Klebsiella pneumoniae	2019	KPC-17	8	8	16	16	16	8	4	4	16	4	16	64
Klebsiella pneumoniae	2019	OXA-48	8	1	1	1	1	1	1	4	16	1	16	64
Enterobacter cloacae	2018	IMP-8	4	1	16	16	8	8	1	2	4	4	0.5	16
2020—2021														
Klebsiella pneumoniae	2020	KPC-2	8	8	16	16	16	4	1	2	16	4	16	64
Klebsiella pneumoniae	2020	KPC-2	8	8	16	16	16	4	1	2	16	4	16	64
Klebsiella pneumoniae	2020	KPC-2	32	8	16	16	16	4	4	2	16	4	16	64
Klebsiella pneumoniae	2020	KPC-2	8	8	16	16	16	4	4	2	16	4	16	64
Klebsiella pneumoniae	2020	KPC-2	32	8	16	16	16	4	1	2	16	4	16	64
Klebsiella pneumoniae	2020	KPC-2	8	8	16	16	16	4	1	2	16	4	16	64
Klebsiella pneumoniae	2020	KPC-2	8	8	16	16	16	4	1	2	16	4	16	64
Klebsiella pneumoniae	2020	KPC-91	32	8	16	16	16	4	4	2	16	4	16	64
Klebsiella pneumoniae	2021	OXA-48	8	8	8	16	1	8	1	0.5	2	4	2	32
Klebsiella pneumoniae	2021	OXA-48	32	8	16	16	16	8	1	4	2	4	1	64
Enterobacter cloacae	2021	IMP-8	8	8	16	16	16	8	1	1	1	1	0.25	64
Serratia marcescens	2020	IMP-type	8	8	16	16	16	4	4	2	16	4	16	64

AMK, amikacin; ATM, aztreonam; CAZ, ceftazidime; CBPM, carbapenemase; C/T: ceftozolane/tazobactam; CRO, ceftriaxone; COL, colistin; ETP, ertapenem; FEP, cefepime; IMP, imipenem; LVX, levofloxacin; MEM, meropenem; TZP, piperacillin/tazobactam.

ratio 0.91, 95% CI: 0.55—1.49) of methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci cases. However, there was a non-statistically significant increase observed (incidence rate ratio 1.64, 95% CI: 0.92—2.92; risk ratio 1.08, 95% CI: 0.91—1.29) in the case of resistant Gram-negative organisms, such as CRE, carbapenem-resistant *Pseudomonas aeruginosa*, and multidrug-resistant *Acinetobacter baumannii*.[16] The result was similar to our finding; a general decrease in susceptibility rates to most clinically used antibiotics was observed for Enterobacterales, although the difference did not reach statistical significance. Another possible factor was that the impact of the COVID-19 pandemic on the health care system varied from country to country. During the initial period of the pandemic, a rise in antimicrobial resistance cases was observed in locations heavily impacted by severe or critical COVID-19 cases, such as the USA, Wuhan, China, Italy, France, and Brazil.[14,16,29] SARS-CoV-2 reached Taiwan on January 21, 2020, when the first case was identified in a 50-year-old woman who had been teaching in Wuhan, China. There were 823, 16,303, and 9,167,811 confirmed cases in 2020, 2021, and 2022, respectively.[19] As a result, the scale of the COVID-19 pandemic was relatively small in the first two years during 2020—2021 in Taiwan, with a population estimated at 23.3 million people.[15,19] In a study conducted by Lai et al., the resistance rates of the selected antibiotics in the study remained constant between the two time periods. However, the incidence (per 10,000 inpatient-days) of ampicillin/sulbactam-, imipenem-, and levofloxacin-resistant *A. baumannii* complex infections increased from 43.7, 59.5, and 49.0 in the period of January to June 2019 to 71.4, 86.1, and 75.6 in the corresponding period of January to June 2020, respectively.[15] The study also revealed an increase in antibiotic usage, particularly among patients with severe disease during the COVID-19 pandemic in Taiwan. This rise in antibiotic usage is attributed to the clinical presentations of COVID-19, which resemble bacterial pneumonia, leading clinicians to add broad-spectrum antibiotics empirically. The antibiotic consumption of agents again multidrug-resistant Gram-negative bacillus such as quinolones, carbapenems, and colistin increased by 10.7%, 13.8%, and 23.9%, respectively, during January to June 2020 compared to the same period in 2019.[15] This rise in antibiotic usage is attributed to the clinical presentations of COVID-19, which resemble bacterial pneumonia, leading clinicians to add broad-spectrum antibiotics empirically. Delay or avoidance of medical care due to COVID-19 concern could heighten the risk of morbidity and mortality linked to treatable and preventable health conditions.[32] Even when the number of new COVID-19 cases was low, there was a persistent delay in seeking health care, posing a significant health risk to patients, especially those with chronic conditions.[33] Additionally, the rise in nosocomial BSI during the COVID-19 pandemic can primarily be attributed to increased hospitalizations, longer durations of admission, and the necessity of invasive procedures among COVID-19 patients. Moreover, overwhelmed healthcare systems may struggle to maintain infection control measures, leading to lapses in sterile techniques and higher transmission rates.

Furthermore, immune compromise in severe COVID-19 cases, widespread use of antibiotics, and disruptions to routine care further contribute to the emergence and spread of multidrug-resistant pathogens, increasing the risk of nosocomial BSI.[30–32]

A previous SMART study investigated Enterobacterales isolates causing respiratory tract infection (RTI), complicated urinary tract infection (cUTI), and complicated intra-abdominal infection (cIAI) in Taiwan during 2016–2018. The ertapenem non-susceptible rates were 12.7%, 7.7%, and 5.7% for isolates from RTIs, cUTIs, and cIAIs, respectively.[34] All Enterobacterales were collected from BSI, and the ertapenem non-susceptible rate was 6.1% (75/1231), which was close to those of cUTI and cIAI but less than isolates from RTI. In 2020, According to SMART, ESBL, AmpC, and carbapenemase genes were detected in 40.5% (17/42), 45.2% (19/42) and 11.9% (5/42) of Enterobacterales from cIAIs in Taiwan, respectively.[27] In the present study, the rates of detected carbapenemase genes among patients with BSIs increased from 12.7% (8/63) in 2020 to 20% (12/60) in 2021. In this study, the escalation of antibiotic resistance is chiefly attributed to *K. pneumoniae*. The disparity in antibiotic resistance rates between *E. coli* acquired from community settings and hospitals is not significant. *E. coli* is less frequently carbapenem-resistant than *K. pneumoniae* in many cases due to the latter's higher propensity to acquire and disseminate carbapenemase-producing genes. Previous research revealed that the *K. pneumoniae* plasmid, known as pKPC-LK30 in Taiwan, is missing specific replication origins and lacks the ability to conjugate, limiting its cross-species transfer and contributing to the localized surge in carbapenem-resistant *K. pneumoniae*.[35]

In our study, two novel β-lactamase inhibitor combinations demonstrated preserved *in vitro* efficacy against Enterobacterales. Meropenem-vaborbactam demonstrated slightly higher susceptibility than imipenem-relebactam (99.7% [306/307] vs. 92.8% [285/307]) because the Morganellaceae family, particularly *P. mirabilis* and *M. morganii*, exhibited intrinsic reduced susceptibility to imipenem due to weak affinity of penicillin binding proteins or porin loss, which had a lesser impact on meropenem and ertapenem.[36] Although imipenem-relebactam and meropenem-vaborbactam were not recommended to treat CRE due to OXA-48 by several guidelines, two *K. pneumoniae* isolates with $bla_{\text{OXA-48}}$ were phenotypically susceptible to meropenem-vaborbactam in the present study.[2,37] As of the end of 2023, neither imipenem-relebactam nor meropenem-vaborbactam has received approval from the Taiwan Food and Drug Administration. Consequently, these novel β-lactamase inhibitor combinations have not been utilized in clinical settings up to that point.

Two *E. cloacae* isolates were found to have $bla_{\text{IMP-8}}$; however, both were susceptible to meropenem in our study. In the early 2000s, Yan et al. revealed that 65.0% (13/20) and 90.0% (18/20) of *E. cloacae* carrying $bla_{\text{IMP-8}}$ were susceptible to imipenem and meropenem (MIC $\leq$1 mg/L), respectively, in a university hospital in Taiwan.[38] In a multicentre study during 2010–2012 in Taiwan, 96.3% (26/27) of carbapenemase-producing *E. cloacae* had $bla_{\text{IMP-8}}$. Fourteen of the 37 IMP-8-positive ertapenem-non-susceptible Enterobacterales, including 1 *K. pneumoniae*, 26 *E. cloacae*, 1 *E. coli*, 1 *K. oxytoca*, 4 *C. freundii* and 4 *Raoultella planticola* (37.8%), were susceptible to both imipenem and meropenem *in vitro*.[39] In addition, a national surveillance program in Spain during 2012–2021 also demonstrated that 85.7% (12/24) and 80% (4/5) of IMP-8-positive *K. pneumoniae* and *E. cloacae* isolates were susceptible to meropenem.[40] The imperfect correlation between carriage of $bla_{\text{IMP-8}}$ and carbapenem resistance suggested that the susceptibility test is not a reliable tool for the detection of MβL producers in Enterobacterales. The carriage of $bla_{\text{IMP-8}}$ would be underestimated in the *E. cloacae* complex.

Our study has several limitations. First, only isolates fulfilling the phenotypic resistance selection criteria were included in further molecular detection of resistance mechanisms. Isolates with discordant genotypic and phenotypic resistance results were neglected. Second, the two novel β-lactamase inhibitor combinations were only tested among isolates collected in 2021. The dynamics of the resistance trend could not be compared; however, the two agents had good efficacy in 2021 against Enterobacterales. Finally, resistance mechanisms other than those involving β-lactamase genes, such as porin deficiency or upregulation of efflux pumps, were not performed in this study; therefore, some resistance could not be explained only by the detected β-lactamases.

In conclusion, this study revealed the impact of the COVID-19 pandemic on antimicrobial resistance in Enterobacterales isolates causing bloodstream infections in Taiwan. Although the differences in susceptibility rates did not reach statistical significance, a general trend of reduced susceptibility to most clinically used antibiotics was observed. Notably, there was an increase in the proportion of nosocomial infections during the COVID-19 pandemic, and the detection of ESBL and carbapenemase genes in CRE also showed an upwards trend. The COVID-19 pandemic has brought unprecedented challenges to health care systems worldwide, and efforts to combat antimicrobial resistance must be maintained to prevent the spread of drug-resistant infections.

Data availability statement

The datasets used during the current study are available from the corresponding author upon reasonable request.

Ethics statement

This study was approved by the Institutional Review Board of National Taiwan University Hospital (Taipei, Taiwan) [NTUH 9561709108]. The Institutional Review Board or Research Ethics Committees of each participating hospital approved the SMART program, and informed consent was waived due to the limited minimal risk to the participating patients.

Investigators from the SMART Taiwan Group

Wen-Chien Ko (National Cheng Kung University Hospital, Tainan, Taiwan), Po-Liang Lu (Kaohsiung Medical University Hospital, Kaohsiung, Taiwan), Chun-Eng Liu (Changhua

Christian Hospital, Changhua, Taiwan), Kenneth Yin-Ching Chuang (Chi-Mei Medical Centre, Tainan, Taiwan), Fu-Der Wang (Taipei Veterans General Hospital, Taipei, Taiwan), Yao-Shen Chen (Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan), Min-Chi Lu (Chung Shan Medical University Hospital, Taichung, Taiwan), and Mao-Wang Ho (China Medical University Hospital, Taichung, Taiwan).

Funding

This study was supported by Merck & Co., Inc. (Rahway, NJ, USA).

Declaration of competing interest

All authors have no conflicts of interest to declare.

Acknowledgements

The authors would like to thank all investigators from the SMART Taiwan Group for their time and effort.

References

1. Shields RK, Zhou Y, Kanakamedala H, Cai B. Burden of illness in US hospitals due to carbapenem-resistant Gram-negative urinary tract infections in patients with or without bacteraemia. *BMC Infect Dis* 2021;**21**:572.
2. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). *Clin Microbiol Infect* 2022;**28**:521—47.
3. Amanati A, Sajedianfard S, Khajeh S, Ghasempour S, Mehrangiz S, Nematolahi S, et al. Bloodstream infections in adult patients with malignancy, epidemiology, microbiology, and risk factors associated with mortality and multi-drug resistance. *BMC Infect Dis* 2021;**21**:636.
4. Gouel-Cheron A, Swihart BJ, Warner S, Mathew L, Strich JR, Mancera A, et al. Epidemiology of ICU-onset bloodstream infection: prevalence, pathogens, and risk factors among 150,948 ICU patients at 85 U.S. Hospitals. *Crit Care Med* 2022;**50**:1725—36.
5. Zhou C, Jin L, Wang Q, Wang X, Chen F, Gao Y, et al. Bloodstream infections caused by carbapenem-resistant *Enterobacterales*: risk factors for mortality, antimicrobial therapy and treatment outcomes from a prospective multicenter study. *Infect Drug Resist* 2021;**14**:731—42.
6. Liu YC, Lu CY, Yen TY, Chang LY, Chen JM, Lee PI, et al. Clinical characteristics and outcomes of carbapenem-resistant *Enterobacterales* bacteremia in pediatric patients. *J Microbiol Immunol Infect* 2023;**56**:84—92.
7. Falcone M, Tiseo G, Carbonara S, Marino A, Di Caprio G, Carretta A, et al. Mortality attributable to bloodstream infections caused by different carbapenem-resistant Gram-negative bacilli: results from a nationwide study in Italy (ALARICO Network). *Clin Infect Dis* 2023;**76**:2059—69.
8. Iacchini S, Sabbatucci M, Gagliotti C, Rossolini GM, Moro ML, Iannazzo S, et al. Bloodstream infections due to carbapenemase-producing *Enterobacteriaceae* in Italy: results from nationwide surveillance, 2014 to 2017. *Euro Surveill* 2019;**24**:1800159.
9. Lee YL, Chen HM, Hii IM, Hsueh PR. Carbapenemase-producing *Enterobacterales* infections: recent advances in diagnosis and treatment. *Int J Antimicrob Agents* 2022;**59**:106528.
10. Chen L, Hua J, Hong SJ, Yuan CY, Jing RC, Luo XY, et al. Comparison of the relative efficacy of β-lactam/β-lactamase inhibitors and carbapenems in the treatment of complicated urinary tract infections caused by ceftriaxone-non-susceptible *Enterobacterales*: a multicentre retrospective observational cohort study. *J Antimicrob Chemother* 2023;**78**:710—8.
11. Rigatto MH, Ramos F, Barros A, Pedroso S, Guasso I, Gonçalves L, et al. Double-, single- and none-carbapenem-containing regimens for the treatment of carbapenem-resistant *Enterobacterales* (CRE) bloodstream infections: a retrospective cohort. *J Antimicrob Chemother* 2022;**77**:3118—25.
12. Ohnuma T, Chihara S, Costin B, Treggiari MM, Bartz RR, Raghunathan K, et al. Association of appropriate empirical antimicrobial therapy with in-hospital mortality in patients with bloodstream infections in the US. *JAMA Netw Open* 2023;**6**:e2249353.
13. Wu HY, Chang PH, Chen KY, Lin IF, Hsih WH, Tsai WL, et al. Coronavirus disease 2019 (COVID-19) associated bacterial co-infection: incidence, diagnosis and treatment. *J Microbiol Immunol Infect* 2022;**55**:985—92.
14. Abubakar U, Al-Anazi M, Alanazi Z, Rodríguez-Baño J. Impact of COVID-19 pandemic on multidrug resistant gram positive and Gram-negative pathogens: a systematic review. *J Infect Public Health* 2023;**16**:320—31.
15. Lai CC, Chen SY, Ko WC, Hsueh PR. Increased antimicrobial resistance during the COVID-19 pandemic. *Int J Antimicrob Agents* 2021;**57**:106324.
16. Langford BJ, Soucy JR, Leung V, So M, Kwan ATH, Portnoff JS, et al. Antibiotic resistance associated with the COVID-19 pandemic: a systematic review and meta-analysis. *Clin Microbiol Infect* 2023;**29**:302—9.
17. Sulayyim HJA, Ismail R, Hamid AA, Ghafar NA. Antibiotic resistance during COVID-19: a systematic review. *Int J Environ Res Public Health* 2022;**19**:11931.
18. Cheng SC, Chang YC, Fan Chiang YL, Chien YC, Cheng M, Yang CH, et al. First case of coronavirus disease 2019 (COVID-19) pneumonia in Taiwan. *J Formos Med Assoc* 2020;**119**:747—51.
19. Lai CC, Lee PI, Hsueh PR. How Taiwan has responded to COVID-19 and how COVID-19 has affected Taiwan, 2020-2022. *J Microbiol Immunol Infect* 2023;**56**:433—41.
20. Steinbrook R. Lessons from the success of COVID-19 control in Taiwan. *JAMA Intern Med* 2021;**181**:922.
21. Ng TC, Cheng HY, Chang HH, Liu CC, Yang CC, Jian SW, et al. Comparison of estimated effectiveness of case-based and population-based interventions on COVID-19 containment in Taiwan. *JAMA Intern Med* 2021;**181**:913—21.
22. Sachs JD, Karim SSA, Aknin L, Allen J, Brosbøl K, Colombo F, et al. The Lancet Commission on lessons for the future from the COVID-19 pandemic. *Lancet* 2022;**400**:1224—80.
23. Lob SH, Estabrook MA, DeRyke CA, Alekseeva I, Siddiqui F, Young K, et al. Activity of ceftolozane/tazobactam against clinical isolates of *Pseudomonas aeruginosa* from patients in the Middle East and Africa - study for monitoring antimicrobial resistance trends (SMART) 2017-2020. *Int J Infect Dis* 2022;**125**:250—7.
24. Chang CY, Lee YL, Huang YT, Ko WC, Ho MW, Hsueh PR. In vitro activity of imipenem/relebactam, meropenem/vaborbactam and comparators against Enterobacterales causing urinary tract infection in Taiwan: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART), 2020. *Int J Antimicrob Agents* 2023;**61**:106815.
25. Liu YM, Ko WC, Ho MW, Lee YL, Hsueh PR. *In vitro* activity of imipenem/relebactam, meropenem/vaborbactam and comparators against *Pseudomonas aeruginosa* in Taiwan: results

from the study for monitoring antimicrobial resistance trends (SMART) in 2020. *J Infect* 2023;**86**:66—117.
26. Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing: 33rd informational supplement M100-S33*. Wayne, PA, USA: CLSI; 2023.
27. Lee YL, Ko WC, Hsueh PR. *In vitro* activity of imipenem/relebactam, meropenem/vaborbactam and comparators against *Enterobacterales* from patients with intra-abdominal infections: results of the study for Monitoring Antimicrobial Resistance Trends (SMART) in Taiwan, 2020. *J Microbiol Immunol Infect* 2023;**56**:75—83.
28. Ghosh S, Bornman C, Zafer MM. Antimicrobial resistance threats in the emerging COVID-19 pandemic: where do we stand? *J Infect Public Health* 2021;**14**:555—60.
29. Kariyawasam RM, Julien DA, Jelinski DC, Larose SL, Rennert-May E, Conly JM, et al. Antimicrobial resistance (AMR) in COVID-19 patients: a systematic review and meta-analysis (November 2019-June 2021). *Antimicrob Resist Infect Control* 2022;**11**:45.
30. Ruiz-Garbajosa P, Cantón R. COVID-19: impact on prescribing and antimicrobial resistance. *Rev Esp Quimioter* 2021;**34**:63—8.
31. Ukuhor HO. The interrelationships between antimicrobial resistance, COVID-19, past, and future pandemics. *J Infect Public Health* 2021;**14**:53—60.
32. Czeisler MÉ, Marynak K, Clarke KEN, Salah Z, Shakya I, Thierry JM, et al. Delay or avoidance of medical care because of COVID-19-related concerns - United States, June 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**:1250—7.
33. Wang Z, Tang Y, Cui Y, Guan H, Cui X, Liu Y, et al. Delay in seeking health care from community residents during a time with low prevalence of COVID-19: a cross-sectional national survey in China. *Front Public Health* 2023;**11**:1100715.
34. Jean SS, Lee YL, Liu PY, Lu MC, Ko WC, Hsueh PR. Multicenter surveillance of antimicrobial susceptibilities and resistance mechanisms among *Enterobacterales* species and non-fermenting Gram-negative bacteria from different infection sources in Taiwan from 2016 to 2018. *J Microbiol Immunol Infect* 2022;**55**:463—73.
35. Chen YT, Lin JC, Fung CP, Lu PL, Chuang YC, Wu TL, et al. KPC-2-encoding plasmids from *Escherichia coli* and *Klebsiella pneumoniae* in Taiwan. *J Antimicrob Chemother* 2014;**69**:628—31.
36. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2022 Guidance on the treatment of extended-spectrum β-lactamase producing *Enterobacterales* (ESBL-E), carbapenem-resistant *Enterobacterales* (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*). *Clin Infect Dis* 2022;**75**:187—212.
37. Sy CL, Chen PY, Cheng CW, Huang LJ, Wang CH, Chang TH, et al. Recommendations and guidelines for the treatment of infections due to multidrug resistant organisms. *J Microbiol Immunol Infect* 2022;**55**:359—86.
38. Yan JJ, Ko WC, Chuang CL, Wu JJ. Metallo-beta-lactamase-producing Enterobacteriaceae isolates in a university hospital in Taiwan: prevalence of IMP-8 in Enterobacter cloacae and first identification of VIM-2 in *Citrobacter freundii*. *J Antimicrob Chemother* 2002;**50**:503—11.
39. Wang JT, Wu UI, Lauderdale TL, Chen MC, Li SY, Hsu LY, et al. Carbapenem-nonsusceptible Enterobacteriaceae in Taiwan. *PLoS One* 2015;**10**:e0121668.
40. Cañada-García JE, Grippo N, de Arellano ER, Bautista V, Lara N, Navarro AM, et al. Phenotypic and molecular characterization of IMP-producing Enterobacterales in Spain: predominance of IMP-8 in *Klebsiella pneumoniae* and IMP-22 in *Enterobacter roggenkampii*. *Front Microbiol* 2022;**13**:1000787.